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(54) **Novel 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-ones and thiones and their use in the prevention or treatment of AIDS.**

(57) 5,11-Dihydro-6H-dipyrido[3,2-b:2′,3′-e][1,4]diazepin-6-ones and -thiones useful in the preven tion or treatment of AIDS are disclosed.

DIAZEPIN-6-ONES AND -THIONES

This invention relates to novel 5,11-dihydro-6H-dipyrido[3,2-b:2′,3′-e][1,4]diazepin-6-ones and -thiones and the use of these compounds to combat HIV infection.

The human disease, Acquired Immune Deficiency Syndrome (AIDS), is considered to be caused by the Human Immunodeficiency Virus (HIV), particularly the strain known as HIV-1.

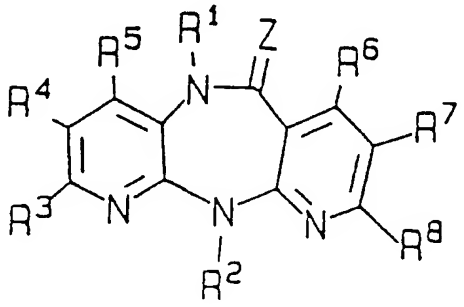
Like other viruses, HIV-1 cannot replicate without utilizing the biosynthetic apparatus of the host cell it infects. The virus causes the biosynthetic apparatus to produce the proteins needed for viral progency. The viral proteins are coded for by the genetic material contained within the infecting virus particle, or virion. In a retrovirus, such as HIV, the stable genetic material normally carried by the virus is RNA, compared to the host cell's DNA genome. The viral RNA must be converted into DNA and integrated into the host cell's genome, so that the host cell may produce the required viral proteins.

The conversion of the RNA to DNA is accomplished by the enzyme reverse transcriptase (RT), which is present within the infecting virion with the RNA. Reverse transcriptase has three identified enzymatic functions -it acts as an RNA-dependent DNA polymerase, as a ribonuclease, and as a DNA-dependent DNA polymerase. As an RNA-dependent DNA polymerase, RT produces a single-stranded DNA copy of the viral RNA. Next, as a ribonuclease, RT releases the newly-formed DNA produced from the original viral RNA and then destroys the original RNA. Finally, acting as a DNA-dependent DNA polymerase, RT makes a second, complementary DNA strand, using the first DNA strand as a template. The two DNA strands form a double-stranded DNA molecule, which is integrated into the host cell's genome by another enzyme called an integrase.

The genetic information of the host cell is stably maintained as double-stranded DNA. In normal protein synthesis, a selected section of the DNA genone is first transcribed into single stranded messenger RNA which is subsequently translated to produce the encoded proteins. There is no reverse transcription involved in the normal metabolism of the host cell and an enzyme displaying a reverse transcriptase activity is not present.

Hence compounds which inhibit the enzymatic functions of HIV reverse transcriptase (especially HIV-1 reverse transcriptase) will inhibit replication of HIV in infected cells without affecting the host cell. Such compounds are useful in the prevention or treatment of HIV infection in human subjects.

Viewed from one aspect, the invention provides compounds of Formula I



(I)

(wherein,

Z is oxygen or sulphur;

R^1 is hydrogen, C_{1-5}alkyl optionally substituted by fluorine, trihalomethyl, C_{3-5}alkenyl or alkynyl, 2-halopropen-1-yl, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl and is optionally substituted by methyl, methoxy or halogen), C_{2-3} alkanoyl or C_{2-4} alkoxyalkyl or alkylthioalkyl;

R^2 is hydrogen, C_{1-5} alkyl optionally substituted by fluorine, C_{2-5}alkenyl or alkynyl, C_{2-4}alkoxyalkyl or alkylthioalkyl, C_{2-4}alkanoyl, C_{2-5}hydroxyalkyl, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, and is optionally substituted by C_{1-3} alkyl or alkoxy, hydroxyl or halogen), phenyl optionally substituted by C_{1-3}alkyl or alkoxy groups, hydroxy or halogen or (C_{1-5}alkoxy)carbonylmethyl; and

R^3, R^4, R^5, R^6, R^7 and R^8 is each hydrogen, or

one of R^3, R^4, R^5, R^6, R^7 and R^8 is an alkyl, alkoxy, alkylthio, alkoxycarbonyl, hydroxyalkyl, alkanoyl, alkanoyloxy, alkanoylamino, carboxyalkyl or aminoalkyl group containing up to 4 carbon atoms, or a

(C_{1-2}alkoxy)carbonyl(C_{1-2}alkyl), mono- or di-(C_{1-2}alkyl)amino, cyano, nitro, hydroxyl, carboxyl, amino, mono- or di-(C_{1-2}alkyl)amino(C_{1-2}alkyl) or azido group or a halogen atom and the remaining five of R^3, R^4, R^5, R^6, R^7 and R^8 are each hydrogen, or

R^3, R^4 and R^5, are each independently hydrogen or C_{1-3}alkyl with the proviso that at least one is hydrogen, or one of R^3, R^4 and R^5 is butyl with the remaining two being hydrogen, and

R^6, R^7 and R^8 are each independently hydrogen or C_{1-3}alkyl with the proviso that at least one is hydrogen, or one of R^6, R^7 and R^8 is butyl with the remaining two being hydrogen;

with the proviso that when R^1 and R^2 are each independently hydrogen or straight-chained or branched C_{1-5}alkyl and R^3, R^4, R^5, R^6, R^7 and R^8 are all hydrogen then Z is sulphur)

and acid addition salts thereof.

Preferred compounds according to the invention include those of Formula I

wherein,

Z is oxygen or sulphur;

R^1 is hydrogen, C_{1-5}alkyl optionally substituted by fluorine, trihalomethyl, C_{2-4}alkenyl or alkynyl, 2-halopropen-1-yl, or C_{2-3}alkoxyalkyl or alkylthioalkyl;

R^2 is C_{1-4}alkyl optionaly substituted by fluorine, C_{2-4} alkenyl or alkynyl, C_{2-4}alkoxyalkyl or alkylthioalkyl, C_{2-3}alkanoyl, C_{2-4}hydroxyalkyl, arylmethyl (wherein the aryl moiety is phenyl or thienyl and is optionally substituted by methyl, methoxy, hydroxyl or halogen), phenyl (optionally substituted by methyl, methoxy, hydroxyl or halogen) or (C_{1-5}alkoxy)carbonylmethyl;

R^3, R^4 and R^5 are each independently hydrogen or methyl, with the proviso that at least one is hydrogen, or R^5 is ethyl, propyl or butyl and R^3 and R^4 are hydrogen, and

R^6, R^7, and R^8 are each independently hydrogen or methyl, with the proviso that at least one is hydrogen, or R^6 is ethyl propyl or butyl and R^7 and R^8 are hydrogen,

and the salts thereof.

Particularly preferred compounds according to the invention include those of Formula I

wherein,

Z is oxygen or sulphur;

R^1 is hydrogen, C_{1-4}alkyl optionally substituted by fluorine or allyl;

R^2 is C_{1-4}alkyl optionally substituted by fluorine, allyl or benzyl; and

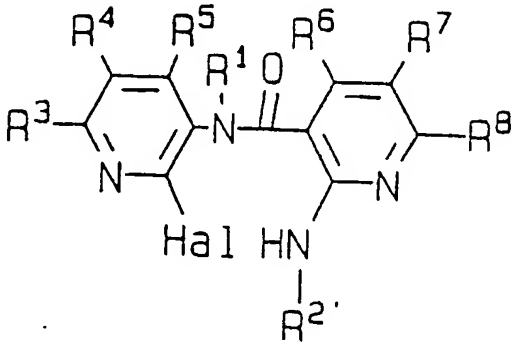
R^3, R^4, R^5, R^6, R^7 and R^8 are each hydrogen,

and the salts thereof.

The compounds according to the invention can be prepared by known methods or modifications thereof.

Thus viewed from a further aspect the invention provides a process for preparing a compound of Formula I or salt thereof, said process comprising at least one of the following steps:

(A) (for preparing compounds of Formula I wherein R^2 is other than hydrogen) cyclizing a carboxylic acid amide of general Formula II

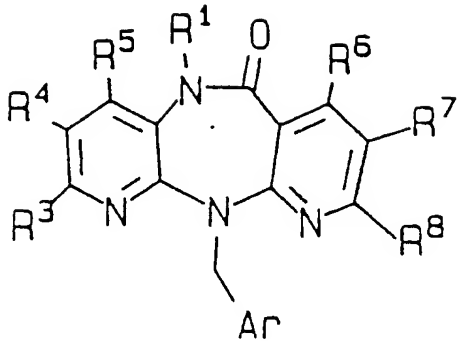


(II)

(wherein R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined, $R^{2'}$ is as defined for R^2 with the exception of hydrogen, and Hal represents a fluorine, chlorine, bromine or iodine atom);

(B) (for producing compounds of Formula I wherein R^2 is hydrogen) hydrolytically cleaving an arylmethyl group from a compound of Formula III

(III)



(wherein R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and Ar represents an aryl group, for example, a phenyl or 4-methoxyphenyl group);

(C) (for preparing compounds of Formula I wherein R^1 is other than hydrogen)

converting a compound of Formula I wherein R^1 is hydrogen into a corresponding 5-alkali or alkaline earth metal compound and subsequently reacting said alkali or alkaline earth metal compound with a compound of Formula IV

$R^{1'}X$ (IV)

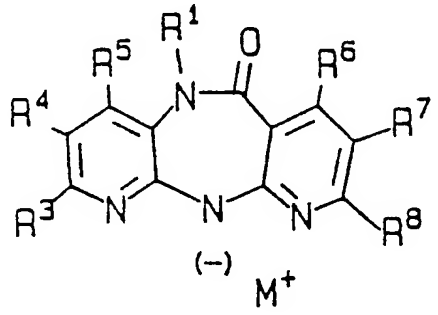
(wherein $R^{1'}$ is as hereinbefore defined for R^1 with the exception of hydrogen and X is the radical of a reactive ester, a halogen atom, a group $OSO_2OR^{1'}$, a methanesulphonyloxy or ethanesulphonyloxy group or an aromatic sulphonyloxy group);

(D) (for preparing compounds of Formula I wherein R^1 is other than hydrogen)

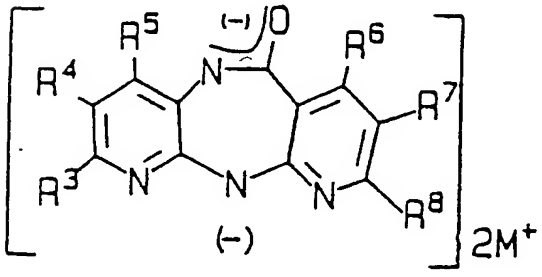
by reacting a compound of Formula I wherein R^1 is hydrogen with a compound of Formula IV (as defined above) in the presence of an amine or an alkali metal carbonate or bicarbonate;

(E) (for preparing a compound of Formula I wherein R^2 is other than an alkanoyl, hydroxyalkyl or alkoxycarbonylmethyl group)

converting a compound of Formula I wherein R^2 is hydrogen into a corresponding metal salt of Formula Va or, where R^1 represents hydrogen, Vb



(Va)



(Vb)

(wherein M represents an alkali metal, such as lithium, sodium, potassium, rubidium or cesium, or M represents the group MgHal+, wherein Hal is chlorine, bromine or iodine) and subsequently alkylating with a compound of Formula VI

$R^{2'}X$ (VI)

(wherein X is as hereinbefore defined) and $R^{2'}$ is as defined for R^2 with the exception of alkanoyl, hydroxyalkyl and alkoxycarbonylmethyl);

(F) (to prepare a compound of Formula I, wherein Z is sulphur)

reacting a compound of Formula I, wherein Z is oxygen, with a sulphurating agent;

(G) subsequently if desired reacting a compound so obtained to

(i) hydrolyse a nitro group to an amino group,

(ii) acylate an amino group to an alkanoylamino group,

(iii) alkylate an amino or aminoalkyl group to a mono- or di-alkylaminoalkyl group,

(iv) acylate the 11-position nitrogen where R^1 is hydrogen, preferably subsequent to step (E); and

(H) converting a compound of Formula I into an acid addition salt thereof or a salt of a compound of Formula I into the free base, where in any of the foregoing steps reactive groups may if desired be protected by protecting groups which are subsequently removed.

In step A, cyclisation is preferably carried out by converting the compounds of Formula II into their alkaline metal salts and subsequent condensation at temperatures between 0 °C and the boiling point of the reaction mixture.

If, in the starting compounds of Formula II, R^1 does not represent hydrogen, metallation requires at least 1 mole of the metallating agent. If R^1 represents hydrogen, at least 2 moles of this agent must be used. For metallation, lithium, sodium and potassium hydrides, lithium alkyls, such as n-butyl lithium, are preferably used.

The reaction is usually carried out in inert solvents, e.g. in tetrahydrofuran, 1,4-dioxane, glycoldimethyl ether, diethyleneglycoldimethyl ether, triethyleneglycoldimethyl ether, dimethylformamide, benzene or anisole. Cyclisation may also be effected by heating carboxylic acid amides of Formula II in dipolar aprotic solvents, preferably in sulfolane or dimethylsulphone. The use of catalytic quantities of strong acids, e.g. sulphuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, polyphosphoric acid, methanesulphonic acid or p-toluenesulphonic acid, has proved to be advantageous. The reaction temperature is generally 110 to 220 °C, the preferred range of temperature being 130 to 170 °C.

In step B, hydrolysis may conveniently be effected by moderate to strong acids or Lewis-acids at temperatures of -20 to +150 °C. Such acids can be, for example, sulphuric acid, methanesulphonic acid, trifluoroacetic acid, trifluoromethanesulphonic acid, phosphoric or polyphosphoric acid. When using phosphoric or polyphosphoric acid, the addition of solvents such as benzene, toluene, phenol, anisole or veratrole has proved to be of advantage.

If Lewis acids, such as aluminium chloride or bromide are used to eliminate the arylmethyl group, solvents such as aromatic hydrocarbons, e.g. benzene, toluene, anisole, or mixtures thereof with dichloromethane are suitable.

It will be obvious to those skilled in the art that Method B is not preferred in those cases wherein any of R^1 and R^3 to R^8 are readily hydrolyzable substituents, for example, wherein R^1 is alkanoyl or any of R^3 to R^8 are alkanoylamino or alkoxycarbonyl. In cases wherein R^1 is alkanoyl or any of R^3 to R^8 are alkoxycarbonyl, for example, it is preferable to utilize Method A described above; when R^1 is hydrogen two equivalents of base must be used. In cases wherein any of R^3 to R^8 are alkanoylamino, for example, it is preferable to carry out the hydrolysis (and subsequent acylation) on the corresponding nitro derivative, and then reduce the nitro moiety to the amine, followed by acylation to yield the desired product.

In step C, the conversion of a compound of Formula I in which R^1 is hydrogen into the corresponding alkali metal or alkaline earth metal compound may be effected by reacting the compound of Formula I with an alkali metal or alkaline earth metal hydroxide, such as lithium hydroxide, barium hydroxide, sodium hydroxide or potassium hydroxide, with an alkali metal alcoholate, such as sodium methanolate or potassium tert-butoxide, with an alkali metal amide, such as sodium amide or potassium amide, or with an alkali metal hydride such as sodium hydride or potassium hydride. The reaction is preferably carried out at elevated temperatures and in the presence of an organic solvent. Inert organic solvents, such as tetrahydrofuran or glycoldimethyl ether are preferred if alkali metal hydrides are used as the metallating agents, whereas, if an alkali or alkaline earth metal hydroxide is used, an aqueous mixture with an organic solvent, such as methanol or tetrahydrofuran, may also be employed. For conversion of the alkali or alkaline earth metal-substituted compound thus obtained into a compound of Formula I in which R^1 is other than hydrogen, the solution or suspension of the alkali or alkaline earth metal compound may be reacted directly, i.e. without isolation, with a compound of Formula IV at -20 °C or at higher temperatures, up to the boiling

point of the solvent or reaction medium, whichever is lower. The substitution takes place almost exclusively at the nitrogen atom in the 5-position of the compound even if R^2 in the starting material of Formula I is a hydrogen atom, provided that one equivalent of base and one equivalent of a compound of Formula IV are used.

It will be obvious to those skilled in the art that the presence of nucleophilic substituents in the end product may require the use of an intermediate of Formula I where R^1 is other than hydrogen having substituents which are, other than the 11-position nitrogen, not nucleophilic but which can be derivatized to yield the required group. For example, amino or monoalkylamino substituents at any of R^3 to R^8 are preferably obtained by alkylating or acylating such an intermediate having a nitro group at any of R^3 to R^8, and subsequently reducing the nitro group, and alkylating, if appropriate, to yield the final product.

In step D examples of amines that may be used include triethylamine, diazabicycloundecene or 4-(dimethylamino)pyridine, and examples of alkali carbonates or bicarbonates that may be used include those such as sodium and potassium carbonate or sodium bicarbonate.

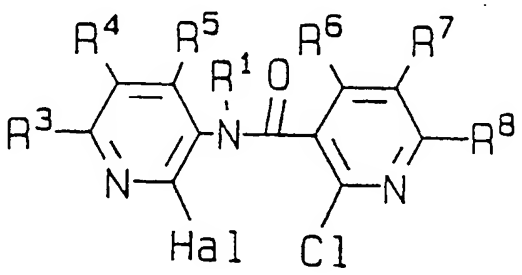
In step E, the conversion of a compound of Formula I into the corresponding alkali metal compound of Formulae Va or Vb may conveniently be effected by reacting with a lithium alkyl (e.g. n-butyl lithium, or t-butyl lithium) optionally in the presence of tetramethylethylenediamine, a lithium dialkylamide, (e.g. lithium diisopropylamide, lithium dicyclohexylamide and lithium isopropylcyclohexylamide), a lithium aryl (e.g. phenyl lithium) an alkali metal hydroxide (e.g. lithium, sodium or potassium hydroxide), an alkali metal hydride (e.g. sodium or potassium hydride), an alkali metal amide (e.g. sodium or potassium amides) or a Grignard reagent (e.g. methyl magnesium iodide, ethyl magnesium bromide or phenyl magnesium bromide). One equivalent or base is required for the formation of compounds of Formula Va, whereas two equivalents of base are required for the formation of compounds of Formula Vb. The metallation is conveniently carried out in an inert organic solvent at temperatures of -78°C and the boiling point of the reaction mixture in question. If a lithium alkyl, lithium aryl, lithium dialkylamide or Grignard reagent is used for the metallation, the preferred solvents are ethers such as tetrahydrofuran, diethyl ether or dioxane, optionally in a mixture with aliphatic or aromatic hydrocarbons, such as hexane or benzene, and the reaction may be carried out at temperatures of -20 to +80°C. When metallation is effected with an alkali metal hydride or alkali metal amide, it is possible to use xylene, toluene, acetonitrile, dimethylformamide and dimethylsulphoxide, in addition to the solvents mentioned hereinbefore, while if an alkali metal hydroxide is used it is also possible to use alcohols such as ethanol, methanol and aliphatic ketones such as acetone, as well as mixtures of these solvents with water.

For conversion of the alkali metal salt thus obtained into a compound of Formula I in which R^2 is other than an alkanoyl, hydroxyalkyl or alkoxycarbonyl methyl group, the solution or suspension of the alkali metal compound may be reacted directly, i.e. without isolation of the reaction product, with a compound of Formula VI at -20°C or at higher temperatures, preferably at the boiling point of the solvent or suspension medium or at the boiling point of the compound of Formula VI, whichever is lower.

It will be obvious to those skilled in the art that the presence of nucleophilic substituents in the end product may require the use of an intermediate of Formula I where R^2 is other than alkanoyl, hydroxyalkyl or alkoxycarbonylmethyl which has substituents other than the 11-position nitrogen, which are not nucleophilic but which can be deprotected to yield the required group. For example, amino or monoalkylamino substituents of R^3 to R^8 are preferably obtained by alkylating or acylating such an intermediate having a nitro group at any of R^3 to R^8 and subsequently reducing the nitro group, and alkylating, if appropriate, to yield the final product.

Methods (A) to (E) are particularly suited to the production of compounds of Formula I in which Z is oxygen, i.e. the diazepinone compounds.

The carboxylic acid amides of Formula II used as starting materials may be obtained, for example, by amination of 2-chloro-nicotinic amides of Formula VII



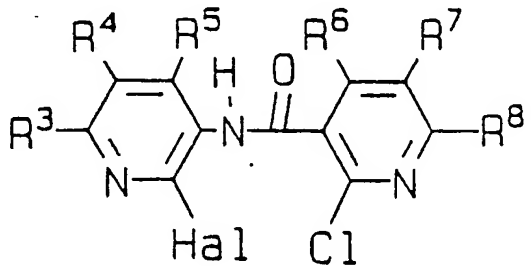
(VII)

(wherein R^1 to R^8 and Hal are as hereinbefore defined) with primary amines of Formula VIII

$H_2N\text{-}R^{2'}$ (VIII)

(wherein $R^{2'}$ is as hereinbefore defined).

The reaction can also be carried out in the presence of inorganic or organic auxiliary bases, such as triethylamine, N,N-dimethylaniline, or sodium or potassium carbonate. The reaction may be carried out without using a solvent; it is preferable, however, to use inert organic solvents at temperatures of 0 °C to 150 °C, preferably at reflux temprature. Suitable inert solvents include an excess of the primary amine of Formula VIII, open chain or cyclic ethers, such as tetrahydrofuran, 1,4-dioxane, glycoldimethyl ether, diethyleneglycoldimethyl ether; aromatic hydrocarbons, such as benzene, toluene, xylene, chlorobenzene or pyridine; alcohols such as methanol, ethanol, isopropanol; dipolar aprotic solvents such as dimethylformamide; 1,3-dimethyl-2-imidazolidinone, 1,3-dimethyl-tetrahydro-2(1H)-pyrimidinone and sulfolane. Starting materials of general Formula VII (wherein R^1 is other than hydrogen) can be prepared from 2-chloronicotinic acid amides of Formula IX



(IX)

by reaction with alklylating agents of Formula IV in the presence of proton acceptors, for example amines, such as triethylamine, diazabicycloundecene, 4-(dimethylamino)pyridine, or alkali or alkaline earth metal hydroxides, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, of alkali carbonates, or alkaline earth metal carbonates or hydrogencarbonates, such as sodium carbonate or potassium carbonate, or potassium hydrogen carbonate.

2-Chloronicotinic acid amides of Formula IX can be obtained by condensation of 2-chloronicotinic acid chloride with 3-amino-2-halopyridines, under well known reaction conditions.

All the other starting materials are known from the literature or may be purchased or may be obtained by procedures known from the literature.

In step F a sulphurating agent such as 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide; bis(tricyclohexyltin)sulphide; bis(tri-n-butyltin)sulphide; bis(triphenyltin)sulphide; bis-(trimethylsilyl)sulphide or phosphorous pentasulphide may be used. The reaction is conveniently carried out in an inert organic solvent such as carbon disulphide, benzene or toluene, at ambient temperature or at an elevated temperature, preferably up to the boiling point of the reaction mixture, and preferably under anhydrous conditions. When using the above mentioned tin or silyl sulphides, it is preferable to carry out the sulphurization reaction in the presence of a Lewis acid such as boron trichloride.

It will be obvious to those skilled in the art that the presence of another carbonyl moiety in a compound of Formula I, for example, a compound wherein Z is oxygen and any of R^3 to R^8 is alkanoyl, will require that the ketone carbonyl be protected via known methods by a suitable protecting group prior to the sulphurization reaction; deprotection subsequent to the sulphurization reaction provides the desired compound. Similarly, in in cases wherein R^2 is, for example, alkanoyl, it will be obvious that the sulphurization reaction should be performed prior to the acylation of the 11-position nitrogen. In those cases wherein the substituents at any of R^3 to R^8 can be derived from nitro, for example, alkanoylamino, the sulphurization reaction can be performed on the corresponding nitro derivative, followed by an appropriate (known) reduction and finally acylation to yield the desired product.

Compounds of Formula I may, if desired, be converted into their acid addition salts, preferably the non-toxic, pharmaceutically acceptable acid addition salts, by conventional methods; for example, by dissolving a compound of Formula I in a suitable solvent and acidifying the solution with one or more molar equivalents of the desired acid. The invention also comprises such salts.

Examples of inorganic and organic acids which may form non-toxic, pharmaceutically acceptable acid addition salts with a compound of Formula I include the following: hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, nitric acid, tartaric acid, citric acid, methanesulphonic acid, and the like. Compounds of Formula I usually. form acid addition salts with one molar equivalent of the acid.

Viewed from a further aspect the invention provides a pharmaceutical composition comprising a compound of Formula I or a physiologically acceptable acid addition thereof together at least one pharmaceutically acceptable carrier or excipient.

The compounds of Formula I or their salts may be administered in single or divided doses by oral, parenteral or topical routes. A suitable oral dosage for a compound of Formula I or a salt thereof would be in the range of about 10 to 500 mg per day. In parenteral formulations, a suitable dosage unit may contain from 1 to 50 mg of said compounds, whereas for topical administration, formulations containing 0.01 to 1% active ingredient are preferred. It should be understood, however, that the dosage administration from patient to patient will vary and the dosage for any particular patient will depend upon the clinician's judgement, who will use the size and condition of the patient as criteria for fixing a proper dosage as well as the patient's response to the drug.

When the compounds of the present invention are to be administered by the oral route, they may be administered as medicaments in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. Such carrier material can be an inert organic or inorganic carrier material suitable for oral administration. Examples of such carrier materials include water, gelatin, talc, starch, magnesium stearate, gum arabic, vegetable oils, polyalkylene-glycols, petroleum jelly and the like.

The pharmaceutical preparations can be prepared in a conventional manner and finished dosage forms can be solid dosage forms, for example, tablets, dragees, capsules, and the like, or liquid dosage forms, for example solutions, suspensions, emulsions and the like. The pharmaceutical preparations may be subjected to conventional pharmaceutical operations such as sterilization. Further, the pharmaceutical preparations may contain conventional adjuvants such as preservatives, stabilizers, emulsifiers, flavour-improvers, wetting agents, buffers, salts for altering the osmotic pressure and the like. Solid carrier material which can be used include, for example, starch, lactose, mannitol, methyl cellulose, microcrystalline cellulose, talc, silica, dibasic calcium phosphate, and high molecular weight polymers (such as polyethylene glycol).

For parenteral use, a compound of Formula I can be administered in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable oil or a mixture of liquids, which may contain bacteriostatic agents, antioxidants, preservatives, buffers or other solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Additives of this type include, for example, tartrate, citrate and acetate buffers, ethanol, propylene glycol, polyethylene glycol, complex formers (such as EDTA), antioxidants (such as sodium bisulphite, sodium metabisulphite and ascorbic acid), high molecular weight polymers (such as liquid polyethylene oxides) for viscosity regulation and polyethylene derivatives of sorbitol anhydrides. Preservatives may also be added if necessary, such as benzoic acid, methyl or propyl paraben, benzalkonium chloride and other quaternary ammonium compounds.

The compounds of this invention may also be administered as solutions for nasal application and may contain in addition to the compounds of this invention suitable buffers, tonicity adjusters, microbial preservatives, antioxidants and viscosity-increasing agents in an aqueous vehicle. Examples of agents used to increase viscosity are polyvinyl alcohol,cellulose derivatives, polyvinylpyrrolidone, polysorbates or glycerin. Microbial preservatives added may include benzalkonium chloride, thimerosal, chlorobutanol or phenylethyl alcohol.

Additionally, the compounds according to the invention can be administered by suppository.

The above described compounds of Formula I possess inhibitory activity against HIV reverse transcriptase. When administered in suitable dosage forms, they are useful in the prevention or treatment of AIDS, ARC and related disorders associated with HIV infection.

Viewed from a yet further aspect, the present invention provides the use of a compound of Formula I or a physiologically acceptable acid addition salt thereof for the manufacture of a therapeutic agent for combatting HIV infection.

Viewed from a still further aspect, the present invention provides a method of treatment of the human body, to combat HIV infection, said method comprising administering to said body a compound of Formula I or a physiologically acceptable acid addition salt thereof.

As stated before, the compounds provided by the invention inhibit the enzymatic activity of HIV RT. Based upon testing of these compounds, as described below, it is known that they inhibit the RNA-dependent DNA polymerase activity of HIV RT. Based upon other testing, not described herein, it is believed that they also inhibit the DNA-dependent DNA polymerase activity of HIV RT.

Utilizing the Reverse Transcriptase (RT) Assay described below, compounds can be tested for their ability to inhibit the RNA-dependent DNA polymerase activity of HIV RT. Certain specific compounds described in the Examples which appear below, were so tested. The results of this testing appears in Table